

Pulmonary arterial hypertension and pulmonary hypertension due to left heart disease: so near and yet so far

To the editor Pulmonary arterial hypertension (PAH) is a heterogeneous clinical condition. Due to its hemodynamic features and pathophysiological mechanisms, it is categorized as a form of precapillary pulmonary hypertension (PH). However, progressive epidemiological changes in the demographic characteristics of individuals with PAH are still providing new nosological insights in clinical practice. The article by Jonas and Kopeck¹ referred to a challenging phenotype of PAH, which still presents a hemodynamic profile compatible with precapillary PH, together with an increased prevalence of risk factors predisposing to left heart disease, particularly to left ventricular diastolic dysfunction. In the analysis involving patients enrolled in the COMPERA (Comparative, Prospective Registry of Newly Initiated Therapies for Pulmonary Hypertension) registry between May 2007 and April 2015, Optiz et al² first coined the term “atypical PAH,” while “PAH with comorbidities” was subsequently provided in the recommendations from the 2nd Cologne Consensus Conference 2018 to alternatively identify this hybrid PH phenotype.³ Although efforts were made to indicate peculiar features defining such a new PH entity, data from the literature suggested possible overlaps between the pathobiological mechanisms of PAH and PH regarding heart failure with preserved ejection fraction (HFpEF). These 2 PH phenotypes have been shown to share a neurohormonal basis predisposing to right ventricular (RV) failure and pulmonary vascular disease. Endothelin-1 (ET-1) has been reported to play a pivotal role in the development of vascular abnormalities in PAH, including pulmonary vasoconstriction, smooth cell proliferation, and vascular remodeling. In contrast, the counterregulatory peptide adrenomedullin is known for its cardioprotective effect on pulmonary circulation, including vasodilatation and inhibition of vascular disruption. The co-upregulation of both these pathobiological pathways has been described in animal models of PAH. Furthermore, their activation

has also been proposed as an early noninvasive marker of pulmonary vascular disease and RV dysfunction in patients with HFpEF. In their analysis, Obokata et al⁴ found higher plasma levels of both C-terminal proET-1 and midregional proadrenomedullin in patients with HFpEF, both at baseline and on exertion. Apart from that, they reported a significant direct correlation with mean pulmonary arterial pressure and pulmonary artery wedge pressure, as well as an inverse relationship with pulmonary arterial compliance.

Another aspect suggesting a potential disease continuum between PAH and PH in HFpEF is a weaker response to targeted PAH-therapy in patients with PAH and concomitant risk factors for left heart disease, which raises suspicion that these factors may potentially contribute to such low therapeutic efficacy. A plausible explanation of the weaker response to treatment takes into account the potential impact of cardiovascular risk factors and comorbidities on developing systemic inflammation and coronary microvascular disease, with subsequent RV impairment, lower exercise tolerance, and nonresponsiveness to PAH-specific drugs, which act mainly on pulmonary circulation. Finally, in patients with atypical PAH, a trend toward higher pulmonary artery wedge pressure and left ventricular end-diastolic pressure was observed, which raise RV afterload and impair RV function.^{2,5}

In conclusion, research on atypical PAH provides new insights suggesting a closer interplay between PAH and PH in HFpEF and offers a hypothesis on a potential disease continuum between these 2 PH phenotypes. Further studies are needed to elucidate a plausible etiological link between PAH and coexisting cardiovascular risk factors in order to stratify the therapeutic response to targeted PAH-treatment in this population.

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Authors' reply We would like to thank Riccardo Scagliola for his interesting comment to our article on a new, challenging phenotype of pulmonary arterial hypertension (PAH), published in the December issue of *Polish Archives of Internal Medicine (Pol Arch Intern Med)*.¹ Although recent advances in treatment contributed to improving prognosis of patients with PAH, this population has in fact changed substantially during the last decades, which has been recently described as a novel phenotype of PAH, atypical PAH, or PAH with comorbidities. More prevalent features of heart failure with preserved ejection fraction (HFpEF) in newly diagnosed patients with pulmonary hypertension (PH) made differential diagnosis more challenging and raised questions regarding a possible overlap between these 2 disease entities (PAH and HFpEF with PH).

As recently shown, the observed shift in the epidemiology of PAH and the higher number of cardiovascular comorbidities in patients with PAH can be associated with an increasing age of diagnosed patients. What is more, some of the main cardiovascular risk factors, including alterations in glucose and lipoprotein metabolism, can serve as prognostic factors and affect patients' survival.²⁻⁴ As reported in the analysis of recent randomized, placebo-controlled trials by Rose et al,⁵ elderly patients were characterized by less severe hemodynamic impairment including lower baseline mean pulmonary arterial pressure and pulmonary vascular disease, despite worse functional impairment and a less favorable response to PAH-specific treatment, than their younger counterparts. This may be partially attributed to the presence of PH with more abundant risk factors for left ventricular diastolic dysfunction, yet

still fulfilling the hemodynamic criteria of a pre-capillary disease. Furthermore, the authors found that older individuals with PAH compared with younger patients were less often diagnosed with idiopathic PAH and more often with PAH associated with connective tissue disease. This accounted for nearly 50% of cases diagnosed in the oldest age group, which may suggest an important role of altered immunity in the etiology of PAH in the elderly.

The definitive distinction between PAH and a postcapillary disease may be challenging, especially considering numerous technical requirements and expertise needed to obtain reliable hemodynamic parameters. In the case of multifactorial diseases, single cutoff values may be insufficient to unequivocally separate disease entities. Additional provocative procedures, including volume loading or exercise challenge, have not been sufficiently validated and thus are not endorsed by the current guidelines. Of note, HFpEF may also affect pulmonary circulation, leading to secondary vascular remodeling, which further reinforces the hypothesis on a spectrum of diseases between HFpEF with PH and PAH.

A growing number of patients with a new phenotype of PH requires comprehensive diagnostic evaluation and close follow-up after initiation of treatment in the expert centers. As recently shown by McLaughlin et al,¹ patients with PAH and a high number of risk factors for HFpEF are characterized by less favorable responsiveness to treatment. This involves drug-associated adverse events and clinical failure occurring in this patient group more frequently than in subjects without comorbidities. Future studies are therefore needed to establish the most appropriate treatment strategies, since this challenging population was often underrepresented or excluded in recent large clinical trial protocols. Analyzing the relationship between age and right heart function during diagnosis and after initiation of treatment may help to further optimize treatment methods in this novel population.

In conclusion, the disparity between an increasing number of patients with a new, challenging PAH phenotype and lack of comprehensive clinical data need to be addressed in future research to establish safe and effective diagnostic work-up and therapeutic strategy for this population.

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